

# Karolinska Institutet/FHI 360\*

## Safe Access: Randomized Trial to Compare Removal Techniques for the One-Rod Subdermal Contraceptive Implant: RemovAid Device versus Standard Approach

### Statistical Analysis Plan

Protocol No: 2018-103

\* This plan was prepared by the lead biostatistician of FHI 360. The plan received additional technical input from the Karolinska Institutet. FHI 360 will be responsible for conducting data analyses for the final clinical study report and for the primary manuscripts for publication.

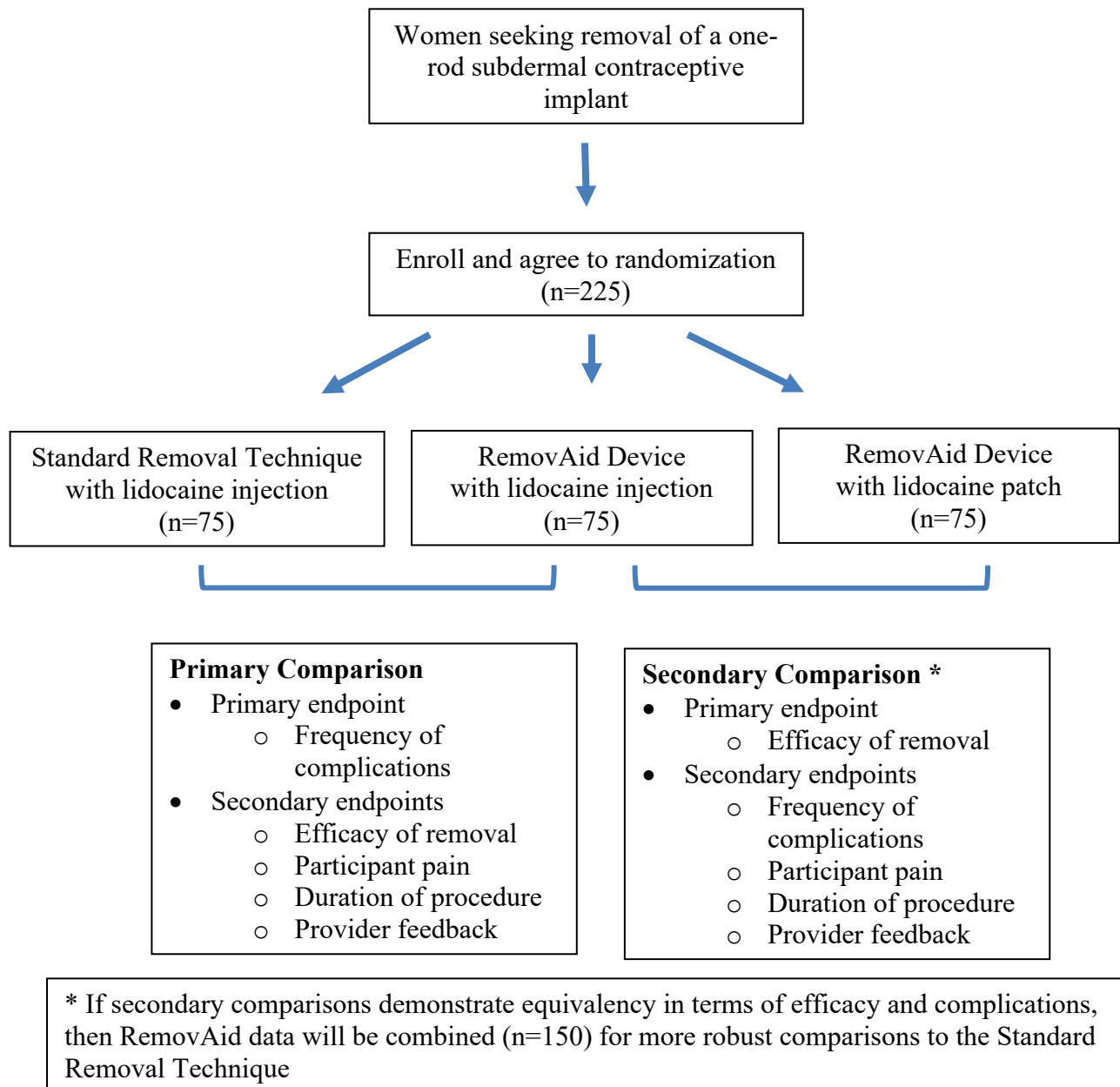
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## 1. INTRODUCTION

This is a single-site randomized clinical trial to compare removal techniques for the single-rod subdermal contraceptive implant. The study will randomize 225 eligible participants in equal numbers to one of three assignments (75 participants in each group): RemovAid Device+lidocaine patch, RemovAid device+lidocaine injection, Standard Removal Technique+lidocaine patch. See figure below.

Figure 1. Study Flowchart



The total duration of the study is expected to be one year. The total duration for each participant is expected to be approximately two weeks. Each woman will have a screening/removal visit and one follow-up visit two weeks after implant removal.

This Statistical Analysis Plan provides details beyond what is specified in the study protocol (version 1.0). Tables, figures and listings shells will be developed and included as an appendix to a future version of this plan.

## 2. STUDY OBJECTIVES

The study objectives described in the protocol flow from the different comparisons that will be made in this trial:

2.1. **Primary Objective:** compare RemovAid device to standard removal technique

- frequency of complications (primary endpoint)
- efficacy of removal, pain from procedure, duration of procedure, and provider feedback (secondary endpoints)

2.2. **Secondary Objectives:** compare RemovAid device/injection to RemovAid device/patch

- efficacy of removal (primary endpoint)
- complications, pain from procedure, duration of procedure, and provider feedback (secondary endpoints)

## 3. STUDY OUTCOMES

The main study outcomes are:

1. Complications
2. Efficacy

The remaining outcomes are:

3. Participant's level of pain from the procedure
4. Duration of procedure (measured in minutes)
5. Provider feedback on the device

## **4. DATA SAFETY AND EFFICACY MONITORING**

An independent, autonomous Safety Review Committee (SRC) has been established by the Karolinska Institutet. The SRC will conduct periodic reviews of study progress indicators and subject safety. It is expected that two (2) such reviews will occur. The project team may also request additional SRC reviews (e.g. should any other findings/issues pertaining to safety or efficacy emerge requiring SRC review outside of the planned periodic meeting dates). The first review will occur after the first 20 removals with the RemovAid device.

The second review will take place halfway through recruitment to determine if the trial should be stopped. If the p-value for a one-sided test of a lower complication rate for the new device is less than 0.0005 (the Haybittle-Peto stopping boundary for superiority) then consideration will be given to stopping the study early and declaring the new device superior to the standard technique. Alternatively, if the p-value for a one-sided test of a lower complication rate in the standard technique is less than 0.025, then consideration will be given to stopping the trial early and declaring that the new device is inferior (i.e. harmful) compared to the standard technique. A final decision whether or not to stop early and declare superiority or harm will be made by the SRC after taking into consideration the pattern of complications, efficacy, and other secondary outcomes. No adjustment will be made to the final p-value for declaring harm or non-inferiority based on this planned interim analysis.

## **5. ANALYSIS POPULATIONS**

Three main analysis populations will be used: intent-to-treat (ITT), treated population, and user population.

The final statistical report will include an accounting of all persons screened, including the number enrolled, the number followed during the study, and other key study status indicators. The reason for excluding any data from any analysis population will be documented.

The general criteria for inclusion/exclusion of participants in these analysis populations are described below. Any changes to these general criteria will be established in blind review by the Karolinska Institutet before locking the database.

### **5.1. Screened Population**

This population consists of all participants screened for the study, including screening failures, eligible participants not enrolled, and participants eventually enrolled. The screened population will be used to estimate what proportion of implant users in the future might be suitable for implant removal using the RemovAid device.

## **5.2. Intent-to-treat (ITT) Population**

This population includes all participants in the screened population who were enrolled and randomized. This is the most inclusive study population for analysis and includes participants who were deemed protocol violations after randomization and or participants who did not undergo a removal attempt (defined as the clinicians' act of handling the removal instruments with intention to remove the subdermal implant), and situations where a removal attempt was not started. Any participant who received the incorrect procedure (due to randomization or allocation error) will be included in the ITT population and analyzed according to initial randomized assignment. The ITT population will mainly be used for analyzing participants' baseline characteristics.

## **5.3. Treated Population**

The Treated Population is a subset of ITT Population and includes only participants who advanced to lidocaine application and then underwent an attempted implant removal procedure. Participants who received the incorrect implant removal procedure are included in this population and analyzed according to the treatment they actually received. This analysis population will mainly be used for evaluating removal results and safety and other secondary endpoints observed during the removal process. Participants' baseline characteristics will be analyzed only if more than 5% of the ITT Population are excluded from the Treated Population.

## **5.4. User Population**

The User Population is a subset of Treated Population who had a successful implant removal. This analysis population will mainly be used for analyzing safety and other secondary endpoints after a successful removal procedure.

## **5.5. Per Protocol (PP) Population**

This is a subset of the User population, excluding all subsequent data collected from participants with a documented protocol violation (either at baseline or during follow-up) that would prevent an accurate analysis of objectives. Participants with random allocation errors will also be excluded. This analysis population will mainly be used for sensitivity analyses of safety, and other secondary endpoints to evaluate the impact of protocol compliance, and only if more than 5% of the User Population are excluded from the PP Population.

## **5.6. Lost to Follow-up Population**

Lost to Follow-up Population is a subset of User Population who have the following experiences:

- left the clinic after implant removal and
- whose last known status was the day of implant removal.

The following table summarizes various analyses conducted on each analysis population.

Table 1: Analyses performed on each analysis population

<b>Population</b>	<b>Eligibility</b>	<b>Baseline</b>	<b>Efficacy</b>	<b>Safety and other secondary endpoints</b>
Screened	✓			
ITT		✓		✓
Treated		✓*	✓	✓†
User		✓		✓
Per protocol		✓		✓***
Lost to Follow-up		✓**		
* Analysis will be performed if > 5% of ITT Population is excluded. ** Analysis will be performed if > 5% of User Population is lost to follow-up. *** Analysis will be performed if > 5% of User Population is excluded. † Analysis will be performed for safety and other secondary endpoints observed during the removal process.				

## 6. GENERAL STATISTICAL ISSUES

All confidence intervals will be two-sided with 95% coverage. Likewise all significant tests will be two-sided and at 0.05 significance level.

Potential outliers will be identified by looking at summary statistics and scatter plots as needed. All outliers will be verified as-such from the source documentation. If excluding one (or several) outlier(s) change(s) the interpretation of the data, two summaries and analyses will be done, one with and one without the outlier(s).

Missing data will be treated as missing at random unless available evidence indicated that missing data is informative. If a participant has missing data at a specific time point, data at all non-missing time points will be used and included in relevant analyses.

All comparisons between treatment groups will be made without adjustment for multiple comparisons. All statistical analyses will be done using SAS® (SAS Institute Inc., Cary) Version 9.4 (or higher).

## 7. STATISTICAL ANALYSIS

### 7.1. Study Participant Disposition and Follow-up

Information about study participant disposition and follow-up during the study will be provided and summarized for each treatment group as follows:

- A flowchart will document the flow of participants through the study and relate this to the different analysis populations;

- Tables will summarize:
  - the number and percentage of participants screened, randomized, removal attempt, successful removal, and removal failure;
  - the reasons for participant non-eligibility for each of the populations;
  - the number and percentage of participants included in each of the analysis populations by study treatment;
  - the number and percentage of total study visits completed, and participant end of study status.

The similarity of participant end of study status between treatment groups will be evaluated using chi-squared tests or Fisher's Exact.

## **7.2. Analysis of Baseline Data**

Baseline variables will be summarized for the ITT, Treated, User, Per Protocol and Lost to Follow-Up Populations under the condition stated previously. The following baseline measures collected at the screening and enrolment visits will be summarized by treatment group:

- Demographic data: age, number of children, weight, height, BMI
- Implant assessment before randomization: visibility of implant contours, past trauma to skin, whole length implant palpability, implant pinchability
- Months since implant insertion, reasons for seeking implant removal, previous removal attempt history

Data will be presented in summary tables by treatment group, site and overall. Categorical variables, and continuous variables that have been categorized at discrete levels, will be summarized by frequencies and percentages. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges, minima and maxima.

## **7.3. Analysis of Primary Endpoint – Frequency of Complications**

The ITT Population will be used for estimating frequency of complications. A supporting analysis will be performed using the Treated and Users Populations. The Per Protocol population will be used if more than 5% of participants in the User Population are excluded.

### **7.3.1. Definition of variables**

Complications will include unusual level of trauma to the skin (bruising/hematoma), excessive bleeding, use of sutures to repair skin after removal, inability to remove the implant, and implant breakage or severing at time of removal. Also, data from the follow-up visit (that occurs two weeks after implant removal) will be used to assess healing of the wound, any subsequent infections, and other complications as may be noted by the investigator.

Frequency of complications will be broken down into the following groups so appropriate comparisons can be made:

- Women in the RemovAid group, separately for lidocaine injection and lidocaine patch
- Women in the Standard Removal group



- Women in the RemovAid group (combining lidocaine injection and patch subgroups)

### **7.3.2. Statistical methods**

The frequency and the percentage of women who experience any complication and specific complications will be tabulated. The percentage of for each of the categories outlined above will be provided by study groups for the entire population. The percentage of women who have complete healing, as assessed at the 2-week follow-up visit, will be tabulated and compared across groups.

## **7.4. Analysis of Secondary Endpoint - Efficacy**

The Treated Population will be used for implant removal efficacy. A supporting analysis will be performed using the Per Protocol Population if more than 5% of participants in the Treated Population are excluded.

### **7.4.1. Definition of variables**

Successful implant removals are defined in the following ways:

- For the standard technique: complete extraction of the implant without breaking the product
- For the experimental device: complete extraction of the implant without breaking the product and without the need for additional tools such as scalpel, tweezers, or forceps.

Efficacy estimates will be broken down into the following groups so appropriate comparisons can be made:

- Women in the RemovAid group, separately for lidocaine injection and lidocaine patch
- Women in the Standard Removal group
- Women in the RemovAid group (combining lidocaine injection and patch subgroups)

### **7.4.2. Statistical methods**

The frequency and the percentage of successful implant removals will be tabulated. The percentage of for each of the categories outlined above will be provided by study groups for the entire population.

## **7.5. Analysis of Other Secondary Endpoints**

The ITT, Treated, and User Populations will be used for analysis of other secondary endpoints.

Three main variables constitute the remaining secondary endpoints:

1. Pain from procedure
2. Duration of procedure
3. Provider feedback on the device

#### **7.5.1. Definition of variables**

Participant's level of pain will be measured using a visual analog scale on a 10cm scale. The level of 0 will correspond to "no pain" while the level of 10 will correspond to "worst pain imaginable". Duration of the procedure will be measured in minutes, from the time when the remove tools are "in hand" to the time when the final bandages are placed. Lastly, provider feedback on the device will primarily be assessed by a Likert scale on the following statement: The RemovAid device helped with the removal procedure (strongly disagree, disagree, neutral, agree, strongly agree).

#### **7.5.2. Statistical methods**

The level of pain will be summarized by means, standard deviations, medians, interquartile ranges, minimum and maximum by each time point, site and study group.

Duration of procedure will be measured in minutes and summarized by means, standard deviations, medians, interquartile ranges, minimum and maximum by each time point, site and study group.

Finally, provider feedback on the device will be analyzed by frequency distribution on the Likert scale as described above.